cinoma. The vast majority of other lesions are usually diagnosed during a surgical procedure or at autopsy. With the advent of more sophisticated diagnostic tools, many of the visceral manifestations of Hippel-Lindau disease that previously would only be found surgically may now be detected by noninvasive methods such as CT scanning.

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Chemically Induced Methemoglobinemia From Aniline Poisoning

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ANILINE HAS LONG been known to be capable of producing methemoglobinemia and a Heinz-body hemolytic anemia.[1-6] Despite decades of experience, the guidelines for therapy for aniline poisoning are not well defined and are somewhat controversial.

Chemically induced methemoglobinemia may be a life-threatening condition, requiring immediate definitive management. Yet, many substances are capable of producing methemoglobin, with varied clinical courses.[7] Similarly, the physiologic state of a patient influences both the symptoms and response to treatment of chemically induced methemoglobinemia.[2,3,8,9]

To manage chemically induced methemoglobinemia properly, a clinician must be aware of its pathophysiology, be adept with the use of reducing agents such as methylene blue, and understand specific physiochemical properties of the toxin. The following case shows the toxicity of one methemoglobin-inducing agent and the possible pitfalls and considerations in the management of chemically induced methemoglobinemia.

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Report of a Case

The patient, a 32-year-old Mexican-American man, arrived at a San Diego emergency room, sweating, apneic and without a pulse after accidentally ingesting 0.3 to 0.6 dl (1 to 2 oz) of Moroso gasoline octane booster. The substance was in a 7-Up container when he mistakenly drank it. He ingested the product about an hour before arriving in the emergency room. The patient had attempted to induce emesis with sea water, but was unsuccessful.

The patient was extremely cyanotic; cardiopulmonary resuscitation instituted immediately upon his arrival successfully revived him and oxygen, naloxone and dextrose were administered. The San Diego Regional Poison Control Center was notified and the toxic component of Moroso was confirmed as 100% aniline. Arterial blood gas studies done while the patient was breathing 100% oxygen from an oxygen mask showed a partial arterial oxygen pressure (Pao_2) of 173 mm of mercury, a partial arterial carbon dioxide pressure ($Paco_2$) of 30 mm of mercury and a pH of 7.39, with an oxygen saturation of 28%. (All oxygen saturation determinations were by direct measurement with an IL 282 Co-oximeter.) A methemoglobin level determination was pending at this time. Because the patient was cyanotic and unresponsive to adequate ventilatory support, and because of the history of aniline ingestion, the diagnosis of methemoglobinemia was assumed.

A 200-mg dose of methylene blue and 500 mg of ascorbic acid were intravenously administered to the patient. Ten minutes later his color improved, he became more lucid and responsive and was able to recall the accident. The initial methemoglobin level determined just before the administration of methylene blue was greater than 70%. (Quantitative methemoglobin was determined by the method of Evelyn and Malloy[10,11] as modified by Henry[12] using a visible spectrophotometer.) One hour after the administration of methylene blue, repeat arterial blood gas analysis showed a Pao_2 of 205 mm of mercury, a $Paco_2$ of 37 mm of mercury, a pH of 7.4 with an oxygen saturation of 63% and a methemoglobin level of 34%.

ABBREVIATIONS USED IN TEXT

G6PD = glucose-6-phosphate dehydrogenase
NADPH = [reduced form of] nicotinamide adenine dinucleotide phosphate

Gastric lavage was done and activated charcoal and a cathartic were then administered. On admission, a complete blood count showed a hematocrit of 50.2%, a hemoglobin level of 17.3 grams per dl and a total leukocyte count of 11,500 per μl.

After receiving 300 mg of methylene blue and 1 gram of ascorbic acid, the patient was transferred to the intensive care unit. Over the next 12 hours, he received an additional 800 mg of methylene blue and 2.5 grams of ascorbic acid intravenously, in five divided doses. The patient appeared alert and oriented, though he had two episodes of nausea and vomiting. Despite his clinical appearance and the subsequent doses of methylene blue and ascorbic acid, the patient's oxygen saturation never exceeded 58% (Table 1). He was transferred to the University of California San Diego Medical Center for continued care.

Examination on admission to UC San Diego Medical Center about 18 hours after exposure to the aniline showed him to be alert, well developed and well nourished and appearing restless. He had cyanotic-appearing skin and dusky blue discoloration of the entire integument, nail beds, mucosal surfaces and conjunctivae. His heart rate was 90 per minute and blood pressure 160/90 mm of mercury. His respiratory rate was 24 per minute, and he had an oral temperature of 37°C (98.6°F). Laboratory studies elicited the following values: hemoglobin, 14.3 grams per dl; hematocrit, 43%; serum bilirubin, total, was 5.2 and direct was 2.9 mg per dl (normal: 1.2, total, and less than 0.2, direct); serum aspartate amino transferase, 195 IU per liter (normal 10 to 30); serum lactic dehydrogenase, 266 IU per liter (normal 25 to 195); blood urea nitrogen, 12 mg per dl (normal 8 to 18), and serum creatinine, 0.9 mg per dl (normal 0.5 to 1.5). Toxicology screening tests done on blood and urine specimens were negative for ethanol, acetaminophen, amphetamines, phenothiazines, salicylates, barbiturates, nonbarbiturate sedative-hypnotics, opiates, cocaine, antihistamines, phencyclidine and heavy metals. Results of arterial blood gas studies done while the patient was receiving 50% oxygen showed a Pao_2 of 207 mm of mercury, $Paco_2$ of 37 mm of mercury, a pH of 7.45 with an oxygen saturation of 53% and a methemoglobin level of 45%.

About 20 hours after the poisoning occurred, the patient received an additional 180 mg of methylene blue, which resulted in a reduction of the methemoglobin level to 24%. Methemoglobin levels declined spontaneously over the rest of his hospital course. His clinical course then became significant for rising bilirubin and amino transferase levels. By the third day after admission, the patient was noted to be very jaundiced and to be simultaneously having a significant reduction in his hemoglobin and hematocrit values (Table 2). Further studies showed an elevated free hemoglobin level of 722 mg per dl (normal 0 to 5), a fall in haptoglobin level to 5.1 mg per dl (normal 60 to 200) and a serum lactic dehydrogenase level of 3,630 IU per liter. A Heinz-body preparation showed the presence of Heinz bodies and spherocytes, supporting the diagnosis of a Heinz-body hemolytic anemia. On the fifth hospital day, a reticulocytosis developed, with an uncorrected reticulocyte count of 3.0%. Direct and

TABLE 1.—*Oxygen Saturation Values, Methemoglobin Levels and Doses of Methylene Blue Administered During the First 22 Hours After Exposure to Aniline*

Time After Ingestion (hours)	Arterial Oxygen Partial Pressure (mm of mercury)	Oxygen Saturation (percent)	Methemoglobin Level (percent of total pigment)	Dose of Methylene Blue (mg)
1.80	173	28.0	>70.0	...
2.08	...	...	...	200
3.00	205	63.0	34.0	...
3.58	...	...	...	100
4.08	Transfer to intensive care unit			
5.17	61	50.0	...	...
6.00	...	...	...	100
6.50	88	56.8	...	...
8.17	144	58.0	...	...
8.50	...	...	...	100
10.25	129	51.0	...	...
11.00	...	...	...	100
11.75	139	49.0	...	...
12.50	...	...	...	200
13.75	118	48.0	...	...
15.50	...	...	...	300
16.50	173	54.2	...	...
18.00	Admission to University Hospital			
18.50	207	53.1	45.0	...
20.00	302	56.8	38.0	...
20.17	...	...	...	180
21.00	...	...	24.0	...
22.00	383	71.2	20.8	...

TABLE 2.—*Hematologic Values*

Days After Ingestion	Hemoglobin (grams per dl)	Hematocrit (percent)	Serum Bilirubin Direct/Total (mg per dl)	Serum AST (IU per liter)	Units of Packed Erythrocytes
Initial	17.3	50.2	.....	...	..
1	14.3	53.0	2.9/ 5.2	195	1
2	13.2	37.0	3.9/ 6.7	140	1
3	11.9	31.0	3.7/ 8.4	135	3
4	11.0	28.0	.....	...	3
5	12.8	35.0	7.6/14.8	247	1
6	13.0	38.0	4.4/ 6.0	214	..
7	13.8	40.0	2.7/ 3.6	217	..
8	...	...	.....	...	..
9	12.8	37.5	1.3/ 1.9	15	..

AST = aspartate amino transferase.

indirect Coombs' tests gave negative values and a glucose-6-phosphate dehydrogenase (G6PD) screening test done on the fourth hospital day showed the presence of the enzyme. Over five days, the patient required nine units of packed red cells. A low-grade fever and sterile pyuria also developed. Empiric antibiotic therapy with ampicillin was given, but results of blood cultures were negative for any pathogens; analysis of urine showed no abnormalities. On discharge the patient's hematologic values had become stable and he was not jaundiced. He was scheduled to return for quantitative G6PD studies but was lost to follow-up.

Aniline Toxicity

Aniline has previously been implicated as a methemoglobin-producing chemical, but the mechanism of action for this response has not been fully elucidated.[7] It has been postulated that a metabolic transformation of aniline to an oxidative metabolite is necessary for the production of methemoglobin.[1,5] Phenylhydroxylamine has been identified as the possible toxic metabolite.[5]

Aniline may be systemically absorbed after either ingestion, inhalation or dermal contact.[1] The minimal toxic dose of aniline has not been fully defined, but Jenkins and co-workers[5] showed a significant elevation in methemoglobin levels in adult volunteers who were given 25 mg of aniline by mouth. The mean lethal dose of aniline has been estimated to be between 15 and 30 grams, though death has been reported after ingestion of as little as 1 gram of aniline.[1,13] Unfortunately, it was impossible to determine the amount of aniline ingested by our patient.

Ingestion of aniline may produce a rapid onset of severe methemoglobinemia as exemplified by the case presented and previously reported cases on aniline poisoning.[6,14] Jenkins and colleagues showed that a peak methemoglobin level occurred two hours after oral administration of 65 mg of aniline to one adult volunteer.[5]

Our patient appeared to be in cardiorespiratory arrest when he came to hospital, a sign consistent with a methemoglobin level of greater than 70%.[2,15,16] However, the cardiac and respiratory effects seen in this patient may have been due partly to the intrinsic toxicity of aniline and its metabolite. Evidence for such intrinsic toxicity has been found in rats and mice, in which both phenylhydroxylamine and aniline produced a ceiling methemoglobin level at doses significantly lower than the lethal dose for either substance.[17,18] Smith and associates reported that in mice that had been given aniline, only a 14% mean methemoglobin level was present at the time of death.[18] This suggests a metabolic conversion to saturation of aniline to its toxic metabolite. If metabolic saturation occurs in humans, prolonged zero-order production of a toxic metabolite would explain the persistence of significant methemoglobin levels up to 20 hours after exposure to aniline in the case reported here, despite initial reduction of the methemoglobin level by administration of methylene blue.

Treatment of Aniline Toxicity

Specific methods for managing chemically induced methemoglobinemia can be classified into five categories: (1) reduction of systemic absorption of the chemical, (2) extracorporeal removal of the chemical, (3) treatment of the "functional anemia" or the hypoxic state with hyperbaric oxygen, (4) reduction of methemoglobin to hemoglobin with the use of reducing agents and (5) replacement of methemoglobin with a functional oxygen-carrying pigment.

Minimizing absorption of aniline after ingestion consists of either the induction of emesis with ipecac syrup in a cooperative, conscious patient or the use of gastric lavage in other situations.[2] It normally takes 20 to 30 minutes for emesis to occur after administration of ipecac syrup.[19] Seizures or coma would contraindicate inducing emesis. Due to the potentially rapid onset of a severe toxic reaction with aniline and the relatively slow onset of the action of ipecac syrup, caution should be exercised with the use of ipecac syrup in acute aniline poisoning.

As in the case reported here, salt water has been shown to be ineffective and potentially hazardous if used as an emetic.[20] A widespread problem encountered with poisoning situations is the prevalence of incorrect, inappropriate and incomplete first-aid information displayed on labels of commercial products.[21] First-aid information on the label of the Moroso octane booster container did suggest the use of "strong salty water" as an emetic.

After gastric evacuation, activated charcoal and a cathartic should be administered to further facilitate removing aniline from the gastrointestinal tract.[2] Because aniline can be absorbed percutaneously, a patient's contaminated clothing should be removed and the skin decontaminated by a thorough washing with soap and water.[2]

Some physicians have tried removing aniline via extracorporeal methods.[6,14,22] The pharmacokinetic indices of aniline are not well defined, however, and the efficacy of its extracorporeal removal is uncertain.

In one case of methemoglobinemia induced by aniline and nitrobenzene, a dramatic reduction in methemoglobin levels occurred after exchange transfusion.[14] The patient had been given methylene blue during the exchange period, however, and quantitative assays for aniline were never done.[14] Therefore, it is impossible to determine the contribution of each modality to a patient's clinical improvement. Advocates of exchange transfusion assert that this procedure has a dual benefit in that in addition to removing a quantity of the toxin, a patient also benefits from the functional oxygen-carrying pigment.[7] Yet we must consider the inherent risks of transfusion, the large volume of blood necessary for this procedure in an adult and the time involved to implement the procedure.

Because aniline and its metabolites are molecules of low molecular weight we should be able to dialyze them. Hemodialysis has been used in the management of aniline poisoning.[6] In one case, after hemodialysis for 7 hours and 20 minutes, 1,300 mg of aniline was removed in the dialysate.[6] The patient's clinical state improved after dialysis, but methylene blue was administered and other supportive measures were used during the dialysis period.[6] Past experience with the use of hemodialysis in aniline poisoning, though limited, suggests that this treatment may have a role in the management of aniline poisoning. But despite the use of hemodialysis in one case, a patient died. In another case, the patient's clinical state deteriorated after dialysis coincident with a massive hemolytic episode.[6,22] Hemodialysis may be indicated for aniline poisoning if a patient's clinical state is deteriorating or not improving despite the use of methylene blue and good supportive and symptomatic management.

Hyperbaric oxygen has been recommended for the treatment of chemically induced methemoglobinemia, but there is no evidence that it is effective and there is little experience with its use.[7,14] Studies with animals using hyperbaric oxygen to treat chemically induced methemoglobinemia have shown conflicting results.[23,24]

Hyperbaric oxygen may allow oxygenation of tissues despite the lack of a normal oxygen-carrying pigment, which could provide time for reduction of methemoglobin to hemoglobin and removal of the offending chemical to occur. With aniline, however, because of its potential for prolonged production of methemoglobin and persistence in the body, hyperbaric oxygen may not be feasible.

The definitive treatment of methemoglobinemia is the use of the reducing agent, methylene blue,[1,7,25] which reduces methemoglobin levels rapidly and effectively.[1] The action of methylene blue is dependent on production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) by the hexosephosphate shunt and the activity of the enzyme, NADPH-methemoglobin reductase.[2,3,26] NADPH is necessary for the reduction of methylene blue to leukomethylene blue,[26] which is responsible for the reduction of methemoglobin to hemoglobin.[26] Hereditary enzymatic defects within the hexosephosphate shunt pathway such as a G6PD deficiency lead to impairment of the ability to produce NADPH within erythrocytes.[3] Consequently, the ability of methylene blue to reduce methemoglobin can be greatly impaired.[3] In fact, because of the oxidative potential of methylene blue, precipitation of a hemolytic episode in persons deficient in G6PD may occur.[3] In one case of aniline-induced methemoglobinemia, a Mexican-American patient with a G6PD deficiency had a negligible response to a therapeutic dose of methylene blue and a Heinz-body hemolytic episode developed.[3]

In the case reported here, the patient showed an apparent tolerance to methylene blue. Despite multiple doses of methylene blue and persistently elevated Pao_2 values, the oxygen saturation failed to increase. The lack of success of methylene blue therapy in this patient could be explained in part by an unrecognized G6PD deficiency. Although we screened the patient for this deficiency, we used blood specimens drawn during an active hemolytic episode. Patients with a G6PD deficiency will show normal G6PD activity as assessed by either a qualitative G6PD screen or by quantitative serologic assay if the test sample is taken while hemolysis is occurring.[27] During active hemolysis, older erythrocytes containing less G6PD are preferentially destroyed, leaving a younger erythrocyte population with a higher G6PD content.[27]

An excessive amount of methylene blue may in itself provoke the formation of methemoglobin because of its own oxidative potential.[16] A total dose of 7 mg per kg of body weight of methylene blue has been previously recommended.[16] A dose of 5 mg per kg of body weight of methylene blue has been reported to produce an elevation of methemoglobin levels.[28] Our patient received a total dose in excess of 15 mg per kg of body weight.

Layne and Smith showed that erythrocytes lose the ability to take up methylene blue in the presence of phenylhydroxylamine.[29] They postulated that phenylhydroxylamine competitively inhibits a process in which a pentose-phosphate shunt mediates NADPH-linked methylene blue uptake by erythrocytes.[29] In the case reported, the patient may have accumulated the aniline metabolite, phenylhydroxylamine, in concentrations sufficient to competitively block the uptake of methylene blue into the erythrocytes.

Administering high doses of methylene blue will produce a blue discoloration of the skin and bodily secretions, inducing an "apparent cyanosis."[30] This may limit a clinician's ability to accurately assess the oxygenation state of a patient by physical examination. In the case reported, the apparent cyanosis noted during the patient's admission examination at UC San Diego Medical Center may have been caused by the methylene blue administered previously.

Although ascorbic acid has been recommended and used as a reducing agent in the management of acute toxic methemoglobinemia, its role is controversial.[1,3,4,7,31] Ascorbic acid has been recommended solely for use in chronic hereditary methemoglobinemia.[1] Opponents of the use of ascorbic acid for acute acquired methemoglobinemia claim that the onset of its reductive action is too slow and it offers little advantage over normal endogenous reduction of methemoglobin.[16,32] Ascorbic acid, a potential urinary acidifier, if administered to a patient with active hemolysis may increase the risk for renal toxic reaction because of an increased potential for precipitation of hemoglobin in acidic urine.[33(p1567),34(p1783)]

Guidelines for Methylene Blue Therapy

The recommended dose of methylene blue for the initial management of methemoglobinemia is 1 to 2 mg per kg of body weight, equivalent to 0.1 to 0.2 ml

per kg of a 1% solution.[2] Maximal response to methylene blue usually occurs within 30 to 60 minutes; therefore, methemoglobin levels should be monitored about an hour after administration of methylene blue.[25] Repeat doses of methylene blue should be spaced at least one hour apart and should only be given after evaluating the response to the last dose. If a patient has a negligible initial response to a therapeutic dose of methylene blue, then G6PD deficiency should be considered. It is advisable to continue to monitor methemoglobin levels even after an initial response to methylene blue because there is the potential for continued production of methemoglobin by aniline.

Continued use of methylene blue should be based on methemoglobin levels in conjunction with the clinical state of a patient. Most patients can tolerate a 30% or less methemoglobin level,[9,15,16] so methylene blue should not be routinely administered on the basis of laboratory values alone. An anemic patient, however, with a methemoglobin level of less than 30% may manifest hypoxic symptoms and consequently would benefit from the administration of methylene blue.

Methylene blue administration should be discontinued if either a negligible response or an increase in methemoglobin levels results after two consecutive doses or if the total dose exceeds 7 mg per kg.

Repeated doses of methylene blue should not be based solely on methemoglobin levels. Considering the inherent toxicity of methylene blue, a patient lacking hypoxic symptoms is a questionable candidate for this treatment.

Secondary Complications

Heinz-body hemolytic anemia has been reported following exposure to aniline.[1,3,6,14] Heinz bodies, aggregates of oxidatively denatured hemoglobin, have been observed in erythrocytes of persons with G6PD deficiency following exposure to oxidative chemicals and in normal persons after exposure to methemoglobin-producing chemicals.[35,36] Excessive doses of methylene blue—that is, more than 15 mg per kg—induced a hemolytic anemia in two infants, one of whom had a normal G6PD determination.[37] In neonates, administration of methylene blue at doses of 2 to 4 mg per kg has induced a Heinz-body hemolytic anemia.[38] This suggests that neonates are probably much more susceptible to the hemolytic action of methylene blue. Adults with a G6PD deficiency may be predisposed to a Heinz-body hemolytic anemia developing if exposed to aniline or given methylene blue.[3] The relationship between the formation of Heinz bodies and methemoglobin with a subsequent hemolytic episode is still unknown.[7] The Heinz-body hemolytic episode in this case could have been attributed to an interplay of factors. Aniline and its oxidative metabolites, excessive methylene blue therapy, or the G6PD status of the patient may have all had a role in the production of a hemolytic anemia.

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